UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,915	09/05/2003	Alan D. Attie	960296.99080	8862

7590 10/31/2006

Nicholas J. Seay
Quarles & Brady LLP
P O Box 2113
Madison, WI 57301-2113

EXAMINER	
SITTON, JEHANNE SOUAYA	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,915	ATTIE ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *4-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-8, and newly added claims 9-11 are pending in the instant application. Claims 4-8 are withdrawn from consideration as being drawn to a non elected invention. Claims 1-3 and 9-11 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The sequence listing filed 8/15/2006 has been entered.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Objection and Rejection

Specification

4. The amendments to the specification, in the reply filed 8/15/2006, to correct the sequence identifiers with regard to SEQ ID NOS 1-4 have overcome the objection made at section 3 of the previous office action.

5. The amendment filed 8/15/2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In table 1, at page 4 of the specification, the

amendment changes the amino acid position from "50" to "52" for the Thr/Ile, B6/BTBR respectively. However, the specification does not appear to provide support for this specific change. At page 12, first paragraph, the response asserts that this change was made to correct an "inadvertent misnumbering". This argument has been thoroughly reviewed but was not found persuasive. As set forth in the MPEP 2163 (I) (B): "While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)." In the instant case, the specification does not appear to provide guidance that the correct amino acid position is 52. While a threonine is present in the hSorCS1 amino acid sequence at position 52, threonine is also present at, for example, amino acid 68, as well as in the different mouse SorCS1 isoforms (see Figure 2). Accordingly, one skilled in the art, based on the guidance in the specification, would not have recognized the existence of the error or the appropriate correction.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

Enablement

6. Amended claims 1-3 and newly added claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Amended claim 1 is drawn to a method of assessing whether a human subject is susceptible to type 2 diabetes by determining the SorCS1 cDNA sequence of that subject, deducing the amino acid sequence encoded thereby, and comparing it with SEQ ID NO: 4, wherein broadly *any* difference indicates that the subject is susceptible to type 2 diabetes. Amended claim 2, is drawn to a method of assessing whether a human subject is susceptible to type 2 diabetes by determining the cDNA sequence of the subject in the SorCS1 gene and comparing it with SEQ ID NO: 3, wherein broadly *any* difference indicates that the subject is susceptible to type 2 diabetes. Amended claim 3 is drawn to a method of determining if a human being is a candidate for developing type 2 diabetes by determining the sequence of the protein coding region of the human SorCS1 in the genome of the human, deducing the amino acid sequence encoded by the region sequenced, and comparing the deduced amino acid sequence to SEQ ID NO: 4, wherein broadly *any* difference indicates the human being is a candidate for developing type 2 diabetes. Newly added claim 9 is drawn to a method of assessing whether a

human subject is susceptible to type 2 diabetes by determining the SorCS1b cDNA sequence of the subject, deducing the amino acid sequence encoded thereby, and comparing it with SEQ ID NO: 4, wherein broadly *any* mutation at residue 52 of the deduced amino acid sequence relative to SEQ ID NO: 4 indicates that the subject is susceptible to type 2 diabetes. Claim 10 is dependent from claim 9 and sets forth that the mutation is any substitution of threonine of the SorCS1b amino acid sequence, while claim 11 sets forth that the specific substitution is isoleucine.

The nature of the invention, therefore, requires the knowledge of predictive associations between any polymorphism or mutation in any protein coding region or cDNA, including position 52 relative to SEQ ID NO: 4, of the human SorCS1 gene and susceptibility to developing type 2 diabetes.

The claims recite "protein coding region" or "cDNA" of the SorCS1 gene, however it is known that in mice, different isoforms of SorCS1 exist. The specification does not teach the different isoforms of human SorCS1. With regard to claims 9-11, the specification does not teach whether SEQ ID NO: 4 is the "SorCS1b" isoform in humans. It is not clear what "differences" with regard to SEQ ID NO: 3 or 4 would be indicative of susceptibility to type 2 diabetes, when different isoforms may exist for human SorCS1.

The specification teaches that the inventors began by narrowing the genetic region associated with severe type 2 diabetes to a 7 MB segment of mouse chromosome 19 (page 4, para 0017). The specification teaches that 2 genes previously found in the region were SorCS1 and SorCS3, which belong to a family sharing a large region of similarity including the VPS10 domain. The specification teaches that due to similarity with sortilin, SorCS1 and SorCS3 are

expected to be involved in insulin-stimulated glucose transportation and in controlling body fat metabolism. The specification teaches that the 7MB region was characterized and that it was found that the only difference between severely diabetic mice and less severely affected mice was 3 mutations in SorCS1, leading to 3 amino acid changes (table 1). The specification, however, does not teach the specific function or activity of SorCS1. The specification does not teach if other mutations occurred in other portions of the mouse genome that may be responsible for the severe form of diabetes observed in the mice.

The specification provides no teaching or working examples of any mutations in any portion of the SorCS1 gene in humans, or an association between SorCS1 alleles in a human subject and type II diabetes susceptibility. The specification asserts at page 3 that the SorCS1 gene in mice is "directly analogous" to the human gene, however this statement is unclear. The genes are not identical, and the meaning of "directly analogous" cannot be determined. For example, at table 1, the specification teaches different mutations at specific positions of mouse SorCS1. The specification teaches a mutation, at position 1139 from Ser to Phe, and at position 1149 from Ser to Pro. However, in humans position 1139 is Glycine, and position 1149 (in SEQ ID NOS 4) is Arginine. None of these amino acids are "directly analogous" to either amino acid found in mice at each position. Although, the specification has been amended to recite a mutation at position 52 from Thr to Ile (also found in SEQ ID NO: 4), the specification provides no teaching of the specific function or activity for SorCS1, or any of these 3 positions, accordingly the affect of each amino acid at such positions is unpredictable. Therefore, given the lack of guidance from the specification as to any mutations in any region of the SorCS1 gene in humans, a teaching of the function or SorCS1 including critical amino acids and domains

required for function, or a predictable correlation between the presence of SorCS1 mutations and diabetes susceptibility in other species, the skilled artisan would be unable to predict an association between any mutation in the protein coding region or cDNA of the SorCS1 gene in humans and susceptibility to type 2 diabetes.

The specification's assertions with regard to putative SorCS1 activity is based on homology analysis with sortilin and the family of proteins that contains a VPS10 domain (page 4, end of para 00017). However, it is known for nucleic acids as well as proteins that even a single nucleotide or amino acid change or mutation can destroy or alter the function of a biomolecule in many instances, albeit not in all cases. The effect of these changes are largely unpredictable as to which ones have a significant effect verses not. The prior art does not teach the function of SorCS1 or how it is involved in type 2 diabetes. The post filing specifically date art provides some characterization of SorCS1 (see Hermey et al, JBC, vol. 278, Feb. 2003, pages 7390-7396), but teaches that neither the mature luminal domain nor any of the cytoplasmic domains of the different SorCS1 isoforms bound any of the ligands previously shown to interact with sortilin and SorLA, demonstrating sorCS1 is functionally different from the previously characterized Vps10-D family receptors (para bridging pages 7390-7391). Additionally, Hermey teaches that the different isoforms of SorCS1 have completely different cytoplasmic domains that mediate different trafficking in cells (abstract). It is clear that the art supports that SorCS1 has a different function than other Vps10 domain family members, and that the 3 different isoforms of SorCS1 do not function in the same manner where the different cytoplasmic domain for each isoform mediates different trafficking in cells.

Newly added claims 9-11 appear to be drafted based on the amended specification's recitation that a difference was found in the SorCS1 gene between B6 and BTBR mice corresponding to amino

acid position 52. The specification asserts "It appears that the activity of the SorCS1 protein may determine islet mass. Alternatively, the SorCS1 protein may affect insulin secretion in pancreatic beta cells or insulin degradation in the kidney or liver" (page 8, para 00033), however the specification does not teach the function of SorCS1, or whether or how the change from Thr to Isoleucine altered the function or activity of the SorCS1 nucleic acid or protein such that the change provides an increased susceptibility to type 2 diabetes in mice. Accordingly, the affect of any mutation at this position, including the mutation of Thr to Ile, is unpredictable in humans. The specification provides no guidance as to whether this mutation, or the other mutations listed in Table 1, occurs in a critical region or domain or how it affects the function or activity of a critical region or domain, such that the skilled artisan would be able to predict which mutations leading to an amino acid changes at this position would provide for the same associations, let alone mutations in other regions. Additionally, the specification provides no teaching or working examples that this mutation, or the other mutations listed in Table 1, exists in humans or would have a similar affect in humans. Kahn teaches that disruption of a specific gene in mouse models of diabetes does not necessarily provide a predictable correlation that any polymorphism in the corresponding human sequence would be similarly associated (Kahn, Cell, vol. 92, pages 593-596, 1998, cited in the IDS). Kahn teaches "Withers et al., reported that disruption of IRS-2 causes diabetes in mice. The most compelling aspect of this report is that inactivation of this single gene causes defects in both insulin action and insulin secretion." (page 593, last para of col. 2). However, Kahn further teaches "The parallels between the IRS-2 knockout mice and Type 2 diabetes in humans raises the tantalizing question as to whether human diabetes is caused by mutations in the IRS-2 gene. Disappointingly, studies in press in several populations, including Danish Caucasians... reveal no

association between polymorphisms in the IRS-2 gene and Type 2 diabetes" (page 594, 2nd full para in col. 2).

The instant specification provides no teaching or guidance as to the role of critical amino acids in any of the isoforms of either murine or human SorCS1 nor how such are involved in susceptibility to type 2 diabetes. The specification provides no predictable association that any alteration, in any protein coding region or cDNA of the SorCS1 gene, in humans, let alone any species, is diagnostic or indicates a susceptibility for developing type 2 diabetes. No common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with type 2 diabetes is provided. Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. No predictable correlation between the structural alterations in the mouse sequence and susceptibility for developing type 2 diabetes has been taught by the specification. Additionally, the specification provides no evidence that any SNP or mutation at such position in humans provides a predictable association with type 2 diabetes. The polymorphisms shown are not representative of the genus of any polymorphism associated with type 2 diabetes because it is not clear which polymorphisms within the SorCS1 gene would have the same affect. The specification does not teach the function of SorCS1 nor how it's function, or lack of function, or altered function are predictably associated with type 2 diabetes.

The quantity of experimentation in this area is extremely large as it requires analysis of each position in the SorCS1 gene, which has not been taught by the specification or the art, to determine whether any alteration at each position is associated with type 2 diabetes. As neither the art nor the specification provide guidance as to which alterations at positions throughout SorCS1 are associated with type 2 diabetes, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible alteration in the SorCS1 gene represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

In order to practice the invention as claimed, one would first have to establish that a predictive relationship exists between mutations in any protein coding or cDNA region of the SorCS1 gene and type 2 diabetes in humans. Further, the scope of the claims requires knowledge of an association between all mutations in the cDNA or the protein coding region, including position 52 relative to SEQ ID NO: 4, of SorCS1 and type 2 diabetes. Due to the scope of the claims, one would be required to further undertake extensive trial and error experimentation with a large number of patients to determine mutations that share a predictive increased susceptibility of type 2 diabetes.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Response to Arguments

7. The response traverses the rejection. The response asserts that the specification is fully enabling because it provides the structural and functional information necessary for one of skill to make a predictive association between mouse and human SorCS1b protein and a mutation in the SorCS1b protein and susceptibility to diabetes in humans. This argument has been thoroughly reviewed but was not found persuasive. The specification provides no correlation between the structure of the specific mutation in Table 1 and their affect on the function or activity of SorCS1 to provide for T2D susceptibility. The specification does not teach the function or activity of SorCS1 nor which regions, domains, or amino acids are responsible for this activity, such that the skilled artisan might be able to predictably correlate which other mutations might have the same affects. The response asserts that applicants disclose that the threonine residue at position 52 in mouse and human SorCS1b is an evolutionary conserved residue and that it is also disclosed that a mutation of the threonine residue in that region is an indicator for a subject's susceptibility to diabetes. This argument has been thoroughly reviewed but was not found persuasive. Although figure 2 provides an alignment between the three isoforms in mice as well as human SorCS1, this alignment provides no analysis regarding regions or domains which are critical to activity or function. The genetic background of the congenic mice and humans would not be expected to be the same. It is not clear, from the teachings in the specification, whether the mutations disclosed in the specification are the cause for the difference in diabetes susceptibility between the B6 and BTBR mice, or whether one or more of the mutations act in concert with or are linked to the causative mutation which could be hundreds or thousands of nucleotides away in a different gene or on a different chromosome.

The response further asserts that "since the same correlation that exists in mice also exists in humans, and since the analogous SorCS1 gene ("b" isoform) having a conserved Threonine at amino acid residue 52 is found in mouse and humans, the same susceptibility to developing T2D should be found in humans and in mouse". The response also asserts that "among the genes analyzed in mice, SorCS1 is the only gene which applicants detected amino acid substitutions and expression level differences". These arguments have been thoroughly reviewed but were found unpersuasive. The meaning of "the same correlation exists in mice also exists in humans" is unclear, because it is not clear which "correlation" is being referred to. The Attorney's arguments cannot take the place of evidence on the record. As stated in the MPEP, 2106

"Arguments of Counsel"

"However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

Additionally, it is not clear from the teachings of the specification, or the assertions in the response, that the only difference in the mice genetically, was that leading to the 3 amino acid differences in table 1, or that the Thr to Ile mutation occurred at position 52. It is additionally unclear, and the specification does not teach whether the Thr to Ile change provided for a difference in activity or function of SorCS1, to establish a predictive association between this amino acid change and T2D in any genetic background. It is also noted that both strains of mice are diabetic. Accordingly, given the lack of guidance in the specification, the skilled artisan would have to perform unpredictable trial and error analysis to perform the methods of the claimed invention as broadly claimed.

Written Description

8. Amended claims 1-3 and newly added claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 1 is drawn to a method of assessing whether a human subject is susceptible to type 2 diabetes by determining the SorCS1 cDNA sequence of that subject, deducing the amino acid sequence encoded thereby, and comparing it with SEQ ID NO: 4, wherein broadly *any* difference indicates that the subject is susceptible to type 2 diabetes. Amended claim 2, is drawn to a method of assessing whether a human subject is susceptible to type 2 diabetes by determining the cDNA sequence of the subject in the SorCS1 gene and

comparing it with SEQ ID NO: 3, wherein broadly *any* difference indicates that the subject is susceptible to type 2 diabetes. Amended claim 3 is drawn to a method of determining if a human being is a candidate for developing type 2 diabetes by determining the sequence of the protein coding region of the human SorCS1 in the genome of the human, deducing the amino acid sequence encoded by the region sequenced, and comparing the deduced amino acid sequence to SEQ ID NO: 4, wherein broadly *any* difference indicates the human being is a candidate for developing type 2 diabetes. Newly added claim 9 is drawn to a method of assessing whether a human subject is susceptible to type 2 diabetes by determining the SorCS1b cDNA sequence of the subject, deducing the amino acid sequence encoded thereby, and comparing it with SEQ ID NO: 4, wherein broadly *any* mutation at residue 52 of the deduced amino acid sequence relative to SEQ ID NO: 4 indicates that the subject is susceptible to type 2 diabetes. Claim 10 is dependent from claim 9 and sets forth that the mutation is any substitution of threonine of the SorCS1b amino acid sequence, while claim 11 sets forth that the specific substitution is isoleucine. Claims 1, 3, and 9-11 accordingly encompass nucleotide variations, such as substitutions, insertions, deletions, and transversions, which change the amino acid sequence of the encoded protein, while claim 2 is not so limited and broadly encompass variations such as substitutions, insertions, deletions, and transversions which do not necessarily alter the sequence of the encoded protein.

The claims recite "protein coding region" or "cDNA" of the SorCS1 gene, however it is known that in mice, different isoforms of SorCS1 exist. The specification does not teach the different isoforms of human SorCS1. With regard to claims 9-11, the specification does not teach whether SEQ ID NO: 4 is the "SorCS1b" isoform in humans. Accordingly, it is not clear

what "differences" with regard to SEQ ID NO: 3 or 4 would be indicative of susceptibility to type 2 diabetes, when different isoforms may exist for human SorCS1.

The specification provides no teaching or working examples of any mutations in any portion of the SorCS1 gene in humans, or an association between SorCS1 alleles in a human subject and type II diabetes susceptibility. The specification asserts at page 3 that the SorCS1 gene in mice is "directly analogous" to the human gene, however this statement is unclear. The genes are not identical, and the meaning of "directly analogous" cannot be determined. For example, at table 1, the specification teaches different mutations at specific positions of mouse SorCS1. The specification teaches a mutation, at position 1139 from Ser to Phe, and at position 1149 from Ser to Pro. In humans position 1139 is Glycine, and position 1149 (in SEQ ID NOS 4) is Arginine. None of these amino acids are "directly analogous" to either amino acid found in mice at each position. The specification has been amended to disclose a mutation at position 52 from Thr to Ile, although no guidance appears to be given regarding this amendment. The specification provides no teaching of the specific function or activity for SorCS1, or any of these 3 positions, accordingly the affect of each amino acid at such positions is unknown. Further, the post filing date art provides some characterization of SorCS1 (see Hermey et al, JBC, vol. 278, Feb. 2003, pages 7390-7396), but teaches that neither the mature luminal domain nor any of the cytoplasmic domains of the different SorCS1 isoforms bound any of the ligands previously shown to interact with sortilin and SorLA, demonstrating sorCS1 is functionally different from the previously characterized Vps10-D family receptors (para bridging pages 7390-7391). It is clear from the teachings of the post filing date art that different isoforms of SorCS1 exist, for which the specification provides no description.

With regard to claims 9-11, the specification does not teach any human SorCS1 sequence or SorCS1b sequence with any of the mutations broadly encompassed by the claims, including an isoleucine instead of a threonine at position 52. The specification teaches that this position was deduced from congenic mice, therefore there is no evidence that this mutation even exists in humans, let alone any mutation at position 52 in human SorCS1. There is no structure/function correlation between the affect of the mutation at position 52, let alone either of the other 2 positions disclosed in table 1 of the specification, found in mice and type 2 diabetes. Accordingly, the disclosure of a single species (threonine to isoleucine) is not representative of the large genus of possible mutations, including substitutions, deletions, transversions, or additions, at position 52 in human or mouse SorCS1 broadly encompassed by the claims.

The specification provides no predictable association that any alteration, in any coding region or cDNA of the SorCS1 gene, in humans, let alone any species, is diagnostic or indicates a susceptibility for developing type 2 diabetes. No common element or attributes of the sequences are disclosed which would permit selection of sequences as mutations or polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with type 2 diabetes is provided. Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. No predictable correlation between the structural alterations in the mouse sequence and susceptibility for developing type 2 diabetes has been taught by the specification. Additionally,

the specification provides no evidence that any SNP or mutation at such position in humans provides a predictable association with type 2 diabetes. The polymorphisms shown are not representative of the genus of any polymorphism associated with type 2 diabetes because it is not clear which polymorphisms within the SorCS1 gene would have the same affect. The specification does not teach the function of SorCS1 nor how it's function, or lack of function, or altered function are predictably associated with type 2 diabetes.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids (different isoforms not taught) and polymorphisms in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms or mutations encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

9. The response traverses the rejection. The response asserts that applicant's do not agree with the examiner's assertion at the top of page 11 that "the specification provides no teaching or

working examples of any mutations in any portion of the SorCS1 gene in human..." because the written description requirement for the application is fully satisfied by the specification which describes the structure of SorCS1 and it's various isoforms in both mice and humans. This argument has been thoroughly reviewed but was not found persuasive. The specification does not teach that any of the mutations listed in Table 1 exists in humans. Further, the specification does not teach that SEQ ID NOS 3 and 4 are directed to the human SorCS1b isoform, nor does it teach any of the corresponding human isoforms to mouse isoforms a and c. Although figure 2 provides an alignment between the three isoforms in mice as well as human SorCS1, this alignment provides no analysis regarding regions or domains which are critical to activity or function. The response asserts that the degree of identity between the mouse and human SorCS1 coding region is "sufficient to soundly predict that applicant's genetic evidence form the congenic mouse model is predictive of the same genetic phenomenon in humans". This argument has been thoroughly reviewed but was not found persuasive. The genetic background of the congenic mice and humans would not be expected to be the same. It is not clear, from the teachings in the specification, whether the mutations disclosed in the specification are the cause for the difference in diabetes susceptibility between the B6 and BTBR mice, or whether one or more of the mutations act in concert or are linked to the causative mutation which could be hundreds or thousands of nucleotides away in a different gene or on a different chromosome.

The response further asserts that it is well known in the art that analogous genes referred to genes similar in function but different in evolutionary origin and asserts that the meaning of "directly analogous" is clear. This argument has been thoroughly reviewed but was not found persuasive. As noted previously and reiterated above, The specification teaches mutations in

mice, at position 1139 from Ser to Phe, and at position 1149 from Ser to Pro. In humans position 1139 is Glycine, and position 1149 (in SEQ ID NOS 4) is Arginine. None of these amino acids are "directly analogous" to either amino acid found in mice at each position.

The assertions made at page 12, para 1 and 2 are addressed in the New Matter rejection below.

The specification further asserts that para 00033 of the specification discloses that the "SorCS1 protein is active in determining islet cell mass, insulin secretion in pancreatic beta cells, or insulin degradation in the kidney or liver". This argument has been thoroughly reviewed but was not found persuasive. Firstly, it is noted that the specification only asserts that the SorCS1 protein "may" determine islet cell mass or "may" affect insulin secretion of degradation. It is not clear, from these teachings, or the remainder of the specification, what the actual function or activity of SorCS1 is, or which regions, domains, or amino acids are critical for such activity or function. The response's assertion that "Hermey's disclosure supports applicant's position that one of skill in the art can use mouse SorCS1b cDNA to identify mutations in the human SorCS1b cDNA and can use it's coding region to predict susceptibility to T2D" is not found persuasive as Hermey does not teach this position. Further, as noted above, the genetic background of the congenic mice and humans would not be expected to be the same. It is not clear, from the teachings in the specification, whether the mutations disclosed in the specification are the cause for the difference in diabetes susceptibility between the B6 and BTBR mice, or whether one or more of the mutations act in concert or are linked to the causative mutation which could be hundreds or thousands of nucleotides away in a different gene or on a different chromosome. Additionally, claims 1-3 are broadly drawn to detecting any difference between

the protein coding region or cDNA of SorCS1 of a human and SEQ ID NO: 4 or 3, respectively, wherein any difference indicates susceptibility to type 2 diabetes or that the subject is a candidate for developing T2D. It is known that different isoforms exist in humans, however it is not clear whether detection of a different isoform would provide for a similar association.

New Matter

10. Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The newly added claims are drawn to "Assessing whether a human subject is susceptible to type 2 diabetes comprising the step of determining the *SorCS1b* cDNA sequence of that [human] subject... and comparing the deduced *SorCS1b* amino acid sequence with SEQ ID NO: 4, wherein a mutation at residue *52*...". Neither the originally filed claims nor the specification appear to provide support for the newly added claims or the recitation of "SorCS1b" cDNA sequence with regard to humans nor the recitation of amino acid 52.

At para 00020 of the specification, the specification generally sets forth diagnostic use for examining humans for their SorCS1 gene and determining differences with respect to SEQ ID NO: 4. Although the specification recites specific positions in Table 1, these positions are with regard to differences found in B6 vs BTBR mice, both of which, were diabetic, albeit with differing severity. However, the specification does not appear to set forth diagnostic methods for

diabetes susceptibility in humans by determining any *particular* mutation or position. Accordingly, the newly added claims directed to diagnostic methods in humans at a specific SorCS1 position appears to introduce new matter into the instantly claimed invention.

Further, with regard to the recitation of "SorCS1b", the specification teaches the SorCS1 a, b, and c isoforms of mouse, but only teach a single SorCS1 sequence for humans (SEQ ID NOS 3 and 4, cDNA and protein respectively). The response does not provide any guidance as to where this recitation is supported in the specification. At page 5, para 00020, the specification discloses examining alleles of the SorCS1 gene of humans, however it does not refer to the SorCS1b isoform. Additionally, the specification does not teach what isoform SEQ ID NO: 4 corresponds to. Likewise, the originally filed claims only recite diagnostic methods with regard to the "SorCS1" sequence in humans, and do not provide support for the SorCS1b isoform. Accordingly, this recitation appears to introduce new matter into the instantly claimed invention.

Additionally, with regard to the recitation of amino acid "52", in table 1, at page 4, the specification was amended to change the amino acid position from "50" to "52" for Thr/Ile, B6/BTBR respectively. However, the specification does not appear to provide support for this specific change. At page 12, first paragraph, the response asserts that this change was made to correct an "inadvertent misnumbering". However, as set forth in the MPEP 2163 (I) (B): "While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)." In the instant case, the

specification does not appear to provide guidance that the correct amino acid position is 52. While a threonine is present in the hSorCS1 amino acid sequence at position 52, threonine is also present at, for example, amino acid 68, as well as in the different mouse SorCS1 isoforms (see Figure 2). Given the limited guidance in the specification, it does not appear that one of skill in the art would not have recognized the existence of the error or the appropriate correction. Accordingly, this recitation appears to introduce new matter into the instantly claimed invention.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
10/27/2006